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Review

The power of automated behavioural homecage technologies in characterizing disease progression in laboratory mice: A review

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ABSTRACT

Behavioural changes that occur as animals become sick have been characterized in a number of species and include the less frequent occurrence of 'luxury behaviours' such as playing, grooming and socialization. 'Sickness behaviours' or behavioural changes following exposure to infectious agents, have been particularly well described; animals are typically less active, sleep more, exhibit postural changes and consume less food/water. Disease is frequently induced in laboratory mice to model pathophysiological processes and investigate potential therapies but despite what is known about behavioural changes as animals become sick, behavioural phenotyping of mice involved in disease studies is relatively rare. A detailed understanding of how behaviour changes as mice get sick could be applied to improve welfare of laboratory mice and support the underlying biomedical research. Specifically, characterizing behavioural changes in ill health could help those working with laboratory mice to recognize when refinements should be introduced, when severity limits are being approached and when humane endpoints should be implemented. Understanding how behaviour changes with illness may also help to identify compounds that have a clinical effect as well as when these agents act. There are an increasing number of automated systems to monitor the behaviour of laboratory mice in their homecages incorporating technologies such as the quantification of cage movement, automated video analysis and radiofrequency identification transponders/readers. Mouse models of neurodegenerative diseases particularly Huntington's disease have been well characterized using these systems and behavioural biomarkers of pathology, including changes in the animals' use of environmental enrichment, changes in food/water consumption and alterations in circadian rhythms, are now monitored by laboratories worldwide and used to refine studies and develop therapies. In contrast, automated behavioural technologies have not been used to characterize the behaviour of mice with systemic diseases such as cancer and liver disease. In this review, common behavioural changes that occur in animals with declining health will be discussed with an emphasis on progressive disease studies involving mice. Automated homecage behaviour recording technologies will then be summarized, studies in which these systems have been used to characterize the behaviour of mice with progressive diseases will be reviewed and the potential to apply automated technologies to refine disease studies involving mice will be discussed.

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Contents

1. Introduction

Laboratory mice (*Mus musculus*) are the most commonly used animals in scientific research; in 2012 74% of scientific procedures carried out on animals within the UK involved mice (Home Office, 2013). In many experimental studies involving mice, disease is induced to model pathophysiological processes and investigate potential therapeutic agents. In accordance with Russell and Burch's 3Rs Principles, when planning a study which would potentially involve the experimental use of animals we should always aim to *replace* laboratory animals with non-sentient alternatives, *reduce* the number of animals used and *refine* experimental procedures to minimize pain and distress (Russell and Burch, 1959). Although there are sometimes unavoidable costs to mice used in disease studies, measures can often be implemented to refine experimental procedures and alleviate pain and/or distress (Committee on Recognition and Alleviation of Distress in Laboratory Animals, 2008). Examples of potential refinements to experimental procedures include the provision of additional care during critical periods of a study, use of the least severe animal experimental model when several models could be used to address a scientific question, improvements to husbandry as well as adherence to both pre-defined severity limits and appropriate humane endpoints.

In progressive disease studies severity limits and humane endpoints are likely to be particularly important in limiting pain and distress (Olsson et al., 2008; Franco et al., 2012a,b; Ashall and Millar, 2013, 2014; Jirkof et al., 2013). Severity limits or justifiable humane endpoints can be defined as a pre-determined set of ethical criteria that allow those working with laboratory animals to recognize when the benefits of the scientific experiment are outweighed by welfare costs to the animal (e.g. the point where the potential scientific benefits of a study are outweighed by the pain or distress induced, EU, 2010). When severity limits/justifiable humane endpoints are met interventions such as analgesic administration or humane killing can be carried out (EU, 2010; Ashall and Millar, 2014). Scientific humane endpoints refer to criteria that allow early termination of experiments before animals experience significant harm while still meeting the experimental objectives (NC3Rs, 2013; Ashall and Millar, 2014). In disease studies, when pain and/or distress are more likely to occur as conditions progress, scientific humane endpoints are implemented to limit disease severity to the minimum required to address an experimental question. Unfortunately both objectively assessing animal welfare and non-invasively measuring disease progression are challenging and can therefore be obstacles to refining disease studies involving mice. Imaging is often advocated as a minimally invasive method of tracking disease progression (Hudson, 2005; Committee on Recognition and Alleviation of Distress in Laboratory Animals, 2008), but anaesthesia is typically required which may affect experimental outcomes and have a welfare cost (Wong et al., 2013). Identifying further behavioural biomarkers of disease progression through cooperation between biomedical scientists and ethologists (Broom, 2006) could therefore help to refine disease studies involving mice. There are also likely to be considerable biomedical benefits to characterizing behavioural changes that occur with disease. There has been increasing concern about animal studies translating poorly to human patients with a contributing factor being that animal studies do not always sufficiently reflect disease in humans (van der Worp et al., 2010). Identification of the mouse models of disease that more closely replicate human disease phenotypes may improve their predictive validity (McGonigle and Ruggeri, 2014). The further use of behavioural analyses to then identify therapies that have a clinical effect on mice may also increase the likelihood of effective translation of studies involving mice to human patients.

The aim here is to review behavioural changes with ill health in mammals with an emphasis on studies involving mice. The potential role of automated homecage behavioural monitoring technologies for characterizing behavioural changes in mice with progressive disease and refining disease studies will then be summarized. Compared to behavioural changes that occur with progressive disease, the automated detection of behavioural changes that occur in pain states have been relatively well described (e.g. Roughan et al., 2009; Miller et al., 2011, 2012; Urban et al., 2011; Wright-Williams et al., 2013; Whittaker and Howarth, 2014), and will therefore not be discussed further here.

2. How does the behaviour of animals change with ill health?

Behavioural changes that occur with ill health have been characterized in a number of species with a range of pathologies. A particularly well characterized series of symptoms collectively referred to as 'sickness behaviours' is frequently seen in animals challenged by infectious

agents. Pyrexia and vasoconstriction typically coincide with changes in posture and active behaviour: some behaviours decrease in magnitude and frequency such as social behaviours, grooming, food consumption and drinking whereas other behaviours such as sleeping increase in magnitude and frequency (Hart, 1988; Aubert, 1999; Weary et al., 2009). These 'sickness behaviours' are a cytokine-driven response to the infectious agents that take place to allow sufficient energy to be conserved so that an immune response can be mounted (Hart, 1988; Aubert, 1999; Dantzer, 2004; Broom, 2006). More recently characterization of behavioural changes with ill health has broadened from focussing largely on 'sickness behaviours' that occur in response to infectious agents, to wider consideration of behavioural changes that may be generalizable across a range of pathologies (Weary et al., 2009). Pathology can be defined as 'the detrimental derangement of molecules, cells and functions that occurs in living organisms in response to injurious agents or deprivations' (Broom, 2006).

There has also been further consideration to the potential adaptive value of the behavioural changes that occur as animals become sick and a growing interest in the capacity for ill animals to express complex behaviours rather than simply assuming behavioural changes always occur due to incapacitation and/or defects arising from illness (Hart, 1988; Aubert, 1999; Weary et al., 2009). This has resulted in further consideration of the motivational changes that are likely to occur as animals get sick (Aubert, 1999) as well as specific hypotheses about the types of behaviours that will be most likely to be affected by pathological changes (Littin et al., 2008; Weary et al., 2009). Weary et al. (2009) predict that behaviours that provide long-term benefits for animals (e.g. play, grooming, exploratory behaviours) are the ones most likely to change with the onset of ill health as animals divert their resources to behaviours critical for short-term survival (e.g. behaviours required for thermoregulation). Similarly Littin et al. (2008) predict that when animals get sick, the use of some resources (e.g. food and water) will be more resilient than the use of others (e.g. resources associated with exploration and play).

2.1. Behavioural changes in mice with disease

Behavioural changes associated with some diseases have been well characterized in laboratory mice using non-automated technologies and these studies provide insight into the types of behavioural changes that would be valuable to detect using automated methods. Changes in activity and exploratory behaviours are common and have been noted in mice with cancer. For example, mice developing SL2 lymphoma spend less time rearing as disease progresses (van Loo et al., 1997). Other common changes include decreased food and water consumption (Jacobsen et al., 2013) which is often accompanied by weight loss, the most frequently measured parameter used to monitor laboratory animals (Dallman, 2000). Healthy rodents invest a large proportion of their waking time grooming which plays a key role in thermoregulation (Gaskill et al., 2013) and also results in considerable water loss through the use of saliva (Hart, 1988; Spruijt et al., 1992). It is therefore perhaps unsurprising that changes in grooming behaviour appear to be particularly common in mice with disease (e.g. van Loo et al., 1997; Paumier et al., 2013). For example, genetically altered mice expressing the human A53T α-syn variant to model Parkinson's disease, groom significantly less than wild-type animals (Paumier et al., 2013). Similarly, mice developing SL2 lymphoma spend less time grooming as disease progresses (van Loo et al., 1997). Changes in the microstructure of grooming patterns have been characterized and linked to anxiety and animal welfare (Kalueff and Touhimaa, 2004). Specifically, uninterrupted self-grooming in a cephalocaudal direction (e.g. mice groom paws, followed by nose/face, head, body, legs then tail/genitals) has been linked to non-stressful/'comfort' situations whereas short bouts of rapid grooming not progressing in a cephalocaudal direction has been linked to stress-invoked states (Kalueff and Touhimaa, 2004).

Many other behavioural changes that occur with ill health involve the animals' use of cage resources. When studying R6/1 mice (a genetically altered strain used to model of Huntington's disease), Littin et al. (2008) observed a significant decrease in the use of cage resources, such as climbing resources and chambers, with disease progression compared to wild-type animals. Impairments in nest building behaviour have been noted in mouse models of Alzheimer's disease (Wesson and Wilson, 2011; Torres-Lista and Giménez-Llort, 2013), Parkinson's disease (Paumier et al., 2013) and prion disease (Cunningham et al., 2003). Similarly, changes in burrowing behaviour (displacing food from a tube in a homecage) occurred in mice with prion disease (Deacon et al., 2001; Cunningham et al., 2003) and colitis (Jirkof et al., 2013). Specifically, burrowing behaviour progressively declined in mice that had been injected with ME7 murine prion homogenate, whereas burrowing in control animals was relatively constant (Cunningham et al., 2003). Similarly, the onset of acute colitis induced by dextran sulphate sodium in the drinking water, caused a significant reduction in burrowing behaviour, e.g. nine days following disease induction mice, mice displaced 50% less of their food compared to control animals, within a 2 h period (Jirkof et al., 2013). Finally, postural changes including adopting a curled up position to conserve body heat (Aubert, 1999) and hunching have also been noted in mice with a number of pathologies including pancreatic cancer and prion disease (Lindsay et al., 2005; Steele et al., 2007b).

3. Why automate the study of behaviour?

Automated behavioural technologies are hypothesized by both Weary et al. (2009) and Littin et al. (2008) as tools likely to improve our capacity to characterize behavioural changes with ill health. Until recently pathology in animals has been detected by direct clinical observation and subjective impression which can lack reliability (Weary et al., 2009). Assessment of laboratory mice by clinical observation/subjective impression is particularly difficult as they are crepuscular (most active during dawn and dusk periods) and therefore behaviours indicative of poor welfare may be most obvious when staffing levels are lowest

(Hawkins, 2002). Similarly, some of the cages used for mice (including opaque and individually ventilated cages) and cage furnishings (including some shelters and nesting materials) may provide barriers to observing the animals (American College of Laboratory Animal Medicine, 2007). Signs of ill health, pain and distress in rodents also tend to be very subtle and it may be adaptive for mice to hide signs of poor health from potential predators (Mayer, 2007).

Potential advantages of behavioural automation compared to manual assessment include continuous and sensitive monitoring (Littin et al., 2008) particularly during dark periods when mice are most active (Steele et al., 2007b; Howerton et al., 2012), and objective measurements can also be obtained because of a lack of observer bias (Spruijt and DeVisser, 2006; Steele et al., 2007b). Automated monitoring often takes place in the absence of humans, which is a key when studying prey species such as mice where stoicism may be adaptive and the presence of humans may mask behavioural indicators of ill health, particularly when pathological changes are mild to moderate (Weary et al., 2009). Automation also greatly reduces the requirement for animal handling which may be stressful and/or confound studies (Tecott and Nestler, 2004; de Visser et al., 2006; Steele et al., 2007b; Winter and Schaefers, 2011). If assessment of the animals using automated technologies is carried out in an enriched and/or complex environment, this is likely to encourage a broad range of species-typical behaviours as well as allowing animals to maintain some control over which resources they invest in (Tecott and Nestler, 2004; Spruijt and DeVisser, 2006; Littin et al., 2008), a key advantage from an animal welfare perspective (Olsson et al., 2003). Examining combinations of behaviours rather than single behaviours is also possible and likely important for behavioural characterization of ill health (Steele et al., 2007b), as is measuring both behavioural and physiological parameters simultaneously (Schaefer and Claridge-Chang, 2012).

There may also be negative aspects of automation, many relating to animal welfare. Some behavioural recording techniques require single housing (Olsson and Westlund, 2007; EU, 2010) or limit the environmental enrichment that can be provided, e.g. minimal bedding is a requirement for some automated behavioural analyses (Steele et al., 2007b). Automation may also encourage high throughput phenotyping which typically involves large numbers of animals (Richardson, 2012) potentially increasing the total number of animals used in scientific research. Similarly, automated systems from different companies may all want to validate their systems using animals (Tecott and Nestler, 2004; Spruijt and DeVisser, 2006) which could also increase numbers of laboratory mice used. The challenges of analysing the large amounts of data generated by automated systems (Tecott and Nestler, 2004; Spruijt and DeVisser, 2006) and transforming data into information that is meaningful in terms of animal health and welfare must also be overcome to harness the true power of automated technologies. Finally, because there are practical and technological limitations with automation, homecage technologies should never be used as a substitute to regular clinical monitoring carried out by experienced, compassionate staff (Hawkins, 2002; Hawkins et al., 2011; Hawkins, 2014) instead be used to provide supplemental monitoring.

4. What are automated behavioural homecage technologies?

Automation has been widely used for a number of years to facilitate the study of individual animals in relatively barren environments, e.g. integrated into open field arenas or non-enriched standard cages. Infrared beam systems which quantify the number of beam breaks to measure activity are frequently used (Talavera et al., 1999; Grillet et al., 2005; Moretti et al., 2005). Infrared sensors which detect body heat are also used to measure activity (Dell'Omo et al., 2002; Ognibene et al., 2005). Implantable radiotelemetry systems with the capacity to measure ECG, heart rate, EEG, body temperature and/or activity have also been used to characterize pathological changes in mice (Arras et al., 2012). Radiotelemetry transmitters are implanted into animals, emitting radio waves that are detected by specific receivers. Technologies most frequently incorporated in automated homecage analysis systems include recording of running wheel rotations, studying cage vibration as a measure of animal movement, automated video analysis and subject (i.e. tag) location by means of radiofrequency identification (RFID) technology. One of the first ways of studying mice in their home environment was through the use of running wheels (Moretti et al., 2005). The running wheel continues to be widely used largely as a measure of activity and/or changes in circadian rhythm (de Visser et al., 2006). Rather than just being a method to assess animals, the presence of running wheels in cages has been shown to greatly effect mouse behaviour, including animals with disease (e.g. Richter et al., 2008), therefore running wheels will not be considered further in this review. In systems that detect floor movement, a homecage can be placed on a platform that measures movement allowing specific behaviours including rearing and grooming to be detected (van der Burg et al., 2008; Benkhelifa-Ziyyat et al., 2013). Automated video analysis techniques used pattern recognition software to detect specific mouse behaviours including rearing, sniffing and hanging (Steele et al., 2007b; Baiguera et al., 2012; Mochel et al., 2012). RFID-based homecage systems typically focus on identifying the animals' location and movement (Lewejohann et al., 2009; Howerton et al., 2012), can be paired with other monitoring equipment such as lickometers (Krackow et al., 2010; Voikar et al., 2010; Bellmann-Sickert et al., 2011) and some systems can be programmed to respond differentially to each mouse and present stimuli such as mild aversive airpuffs (Rudenko et al., 2009). Automated homecage behavioural analysis systems may combine technologies, including systems that detect floor movement, infrared beams, automated video analysis and/or food/water consumption (Goulding et al., 2008; Brodkin et al., 2014).

Table 1
Summary of publications using automated homecage technologies to monitor mice with disease.

Technology	Commercially available?	Company – product	Individual or group housed	Reference	Disease(s) studied	Characterization of genetically altered mice	Key behavioural changes
Systems that detect floor movement	Yes	Metris – Laboras	Individual	van der Burg et al. (2008)	Huntington's disease	Yes (R6/2)	Food consumption
				Wood et al. (2008)	Huntington's disease	Yes (R6/2)	Activity and water consumption
Automated video analysis	Yes	CleverSys – HomeCageScan	Individual	Steele et al. (2007a)	Prion disease	No	Activity, grooming, hanging.
				Steele et al. (2007b)	Prion disease	No	Activity, changes in circadian rhythm, rearing, sniffing.
				Steele et al. (2007b)	Huntington's disease	Yes (R6/2)	Activity, changes in circadian rhythm, grooming, hanging, stretching, jumping.
				Steele et al. (2007c)	Prion disease	No	Activity, grooming, hanging.
				Steele et al. (2008)	Prion disease	No	Activity, rearing, grooming.
				Mochel et al. (2011)	Huntington's disease	Yes (R6/2)	Grooming, jumping, hanging
				Mochel et al. (2012)	Huntington's disease	Yes (R6/2)	Hanging, food consumption
		Noldus – Ethovision	Individual	Baiguera et al. (2012)	Parkinson's disease	Yes (NF-kB/cRel)	Activity
	No		Individual	Zarringhalam et al. (2012)	Huntington's disease	Yes (R6/2)	Changes in circadian rhythm, hanging, rearing, climbing.
Radiofrequency identification (RFID) technology	No		Group	Lewejohann et al. (2009)	Alzheimer's disease	Yes (CRND8)	
RFID, water consumption and operant capabilities	Yes	TSE – IntelliCage	Group	Rudenko et al. (2009)	Huntington's disease	Yes (R6/2)	Exploratory activity, changes in circadian rhythm, drinking and cognitive deficits.
			Group	Codita et al. (2010)	Alzheimer's disease	Yes (tg-ArcSwe)	Exploratory activity, water, cognitive deficits
			Group	Too et al. (2014)	Recovery from pneumococcal meningitis	No	Activity, changes in circadian rhythm and cognitive deficits.
RFID, water consumption, video and operant capabilities	Yes	PsychoGenics – Phenocube	Group	Oakeshott et al. (2011)	Huntington's disease	Yes (BAC)	Activity, changes in circadian rhythm, exploratory activity, rearing and climbing.
			Group	Balci et al. (2013)	Huntington's disease	Yes (R6/2) Yes (BAC)	Activity, rearing, climbing Activity, drinking, rearing, climbing and cognitive changes.

5. Assessment of disease progression using automated behavioural analysis

The number of automated homecage analysis systems is rapidly growing and there are now numerous studies using these technologies to study pathological changes in mice (Table 1). Criteria for studies included in this review consisted of characterization of a progressive disease in laboratory mice where homecage monitoring took place for at least 24 h of continuous monitoring per session.

The application of automated homecage technologies to study behavioural changes in laboratory mice with disease varies greatly with condition (Table 1). Neurodegenerative diseases in mice have been the only conditions characterized by automated technologies with the majority of studies examining genetically altered mouse models of Huntington's disease (Steele et al., 2007b; van der Burg et al., 2008; Wood et al., 2008; Rudenko et al., 2009; Mochel et al., 2011; Oakeshott et al., 2011; Mochel et al., 2012; Zarringhalam et al., 2012; Balci et al., 2013). Huntington's disease is characterized by a progressive decline in cognitive and motor functions and patients frequently suffer from sleep disturbances and affective disorders (Rudenko et al., 2009; Mochel et al., 2011; Balci et al., 2013). Other neurodegenerative disease that have been behaviourally characterized using automated technologies include mouse models of prion disease (Steele et al., 2007a,b,c, 2008), Parkinson's disease (Baiguera et al., 2012; Paumier et al., 2013), Alzheimer's disease (Lewejohann et al., 2009; Codita et al., 2010) and meningitis (Too et al., 2014). Cognitive impairments and affective disorders occur in all of these neurodegenerative diseases. Prion diseases are characterized by ataxia whereas Parkinson's disease is characterized by tremor. The behavioural changes most widely detected by automated technologies include changes in activity (particularly exploratory behaviours and circadian rhythms), changes in food and water consumption as well as changes in self-grooming behaviours.

Using automated homecages, hypoactivity was detected in a number of mouse models of disease including genetically altered models of Huntington's disease (Oakeshott et al., 2011). Compared to wild-type control animals, BAC Huntington's Disease transgenic mice spent significantly more time immobile at both 42 and 60 weeks of age. In contrast, activity did not vary between genetically altered mouse models of Alzheimer's disease compared to wild-types (Lewejohann et al., 2009) and mice with prion disease were hyperactive at disease onset, e.g. from 4 months post-inoculation; prion-infected mice walked the equivalent of ten times further than control animals (Steele et al., 2007b). Given the relatively small number of studies using automated homecage technologies to characterize disease progression in mice (e.g. there is often only one study per disease), it is currently difficult to determine whether the differences detected are actual differences between different disease states, artefacts or the result of the choice of timepoints sampled. Changes in circadian rhythm were commonly seen in mouse models of Huntington's disease (Steele et al., 2007b; Wood et al., 2008; Rudenko et al., 2009; Oakeshott et al., 2011; Zarringhalam et al., 2012). By twelve weeks of age, an altered circadian rhythm activity was seen in R6/2 mice with hypoactivity during the dark phase and hyperactivity in the light phase (Rudenko et al., 2009). Similarly, at 42 weeks of age, there was a lengthened circadian cycle in BAC Huntington's Disease transgenic mice (Oakeshott et al., 2011). Changes in behaviour were also frequently specific to either the dark or light period. R6/2 mice were found to be less active during the light phase than wild-type controls at 7 and 10 weeks of age (Wood et al., 2008) and spent less time resting during the dark phase at 10–11 weeks (e.g. 60% of the dark period resting in R6/2 mice compared to 80% in wild-types) (Zarringhalam et al., 2012). By 12 weeks, R6/2 mice spent significantly less time hanging vertically compared to wild-types during the dark period (Steele et al., 2007b). Behavioural changes specific to time of day were also seen in mice with prion disease; at 5 months post-inoculation, compared to control animals, mice with prion disease spent significantly less time resting during the dark period, whereas time spent resting during the light period was similar (Steele et al., 2007b).

Changes in exploratory activity and behaviours that allow animals to learn about their environment were also frequently detected by automated homecage behavioural technologies. At 4 months of age, prior to the presence of pathological plaques in the brain, transgenic mouse mice expressing mutant amyloid precursor protein (APP) to model Alzheimer's disease carried out approximately 35% fewer exploratory visits when introduced to a novel automated homecage compared to wild-type mice (Codita et al., 2010). Similarly, a decrease in non-nutritive/exploratory visits to drinking areas was also noted in mouse models of Huntington's disease with disease progression (Rudenko et al., 2009; Oakeshott et al., 2011). For example, by 13 weeks of age approximately half of the visits made to drinking areas were non-nutritive/exploratory in wild-type mice, whereas in R6/2 mice approximately 25% of visits were non-nutritive (Rudenko et al., 2009).

Changes relating to food and water consumption were also detected in mice with neurodegenerative diseases housed in automated homecages. Changes in consummatory behaviours, included an increased time spent drinking in R6/2 mice, e.g. an increase compared to wild-types was noted at 10 weeks (Wood et al., 2008) and by 13 weeks R6/2 mice spent more than twice as long drinking compared to controls (Rudenko et al., 2009). Similarly, from 10 weeks of age R6/2 mice spent approximately twice as long eating compared to wild-type controls (van der Burg et al., 2008) and had more frequent feeding bouts at 12 weeks (Mochel et al., 2012). A reduction in water consumption was seen in APP mouse models of Alzheimer's disease at 4 months of age (Codita et al., 2010).

As predicted, progressive disease often affects self-grooming behaviour and this could be detected by some automated homecages. By 5.5 months post-inoculation, mice with prion disease spent approximately half as much time grooming compared to controls (Steele et al., 2007b). In contrast, models of Huntington's disease were associated with more frequent grooming (Steele et al., 2007b; Mochel et al., 2011) at some stages of disease progression, e.g. by 13 weeks of age R6/2 mice spend approximately

twice as long grooming as wild-type controls (Steele et al., 2007b). These studies characterized grooming by quantifying the frequency and duration of self-grooming rather than recognizing specific patterns and sequences in grooming behaviour elements. This may be problematic due to the complexity of the relationship between self-grooming behaviour and animal welfare (particularly relating to anxiety). Self-grooming is likely to increase under two opposite conditions: those of low and high stress. 'Low-stress comfort grooming' typically occurs at the transition from rest to activity and is characterized by long bursts of grooming activity in a cephalocaudal direction, in contrast to 'stress-evoked grooming' which is characterized by frequent bursts of short grooming activity (Kalueff and Touhimaa, 2004). Newer technologies with the capacity to recognize where the animal is grooming (Brodkin et al., 2014) and distinguish between the two types of grooming behaviour (Kyzar et al., 2011) may be more applicable to the characterization of ill health as well also providing an insight into the animal's affective state.

Several studies detected cognitive changes in neurodegenerative diseases (Rudenko et al., 2009; Codita et al., 2010; Balci et al., 2013; Too et al., 2014), for example using RFID-based homecages such as the IntelliCage, which are capable of responding differentially to each mouse that carry out tests like place avoidance when an animal learns to avoid an aversive airpuff. At 9 weeks of age, R6/2 mice demonstrated less avoidance of the location of the cage associated with airpuffs, which may indicate deficits in short-term memory (Rudenko et al., 2009). Given the growing awareness of the close association between physiological, cognitive and affective changes in chronic inflammatory diseases (D'Mello and Swain, 2011), detecting these changes is likely to be an important area for future research.

6. Conclusions

Studies using automated homecage technologies to study mice with disease largely support a priori predictions that 'luxury' behaviours associated with longer-term fitness such as exploratory activities and grooming are the behaviours most likely to change with ill health alongside changes in the ways mice eat and drink. Until now published reports have described behavioural changes in mice with neurodegenerative diseases (particularly Huntington's disease) and the potential to use these technologies to characterize mouse models of other diseases is yet to be determined. Due to technical limitations (e.g. automated video analysis has not been able to discriminate multiple mice in the same cage) social behaviours have not been closely examined using automated technologies. In recent years an area of considerable interest has been to integrate automated video analysis with RFID technology. This would allow the power of both technologies to be combined taking advantage of the capacity to detect detailed behaviours with automated video analysis and the ease of studying socially housed mice with RFID transponders/readers. Automated video analysis and RFID technology have now been successfully combined to study healthy mice (Weissbrod et al., 2013) and work applying this integrated technology to study pathology in mice is likely to be forthcoming. These future directions indicate considerable potential for automated homecage technologies to be used carefully to refine disease studies involving mice and support biomedical science.

Conflict of interest

The author has no conflicts of interest associated with this publication.

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